REMARKS

Claims 1 and 11 are pending in the application. Claims 2-10, and 12-20 have been withdrawn from consideration. Claims 1 and 11 are amended. Claim 11 has also been amended to more properly depend from pending claim 1. Support for these amendments is found throughout the specification, as set forth below. It is believed that no new matter is added by these amendments. In light of these amendments and the following remarks, Applicants respectfully request entry of these amended claims and reconsideration of this application.

Co-pending Application

Applicants herewith provide a copy of co-pending application SN 09/754,809 and the corresponding claims to the USPTO for the purpose of review by the examiner of record.

Specification

The Examiner has objected to the specification, alleging that the paragraphs in the present specification use trademarks and as such the proprietary nature of the marks should be respected. Applicants herein amend the paragraphs containing the trademarks so that they properly identify the marks. Applicant believes this objection has been overcome and respectfully request its withdrawal.

The Examiner has objected to the specification for the recitation of "CYGG" on page 28, line 27, and page 29, line 9 and the recitation of "LXCC" on page 49, line 29 and page 51, line 18. In particular, the Examiner asserts that the identified sequences must be identified by a SEQ ID Number as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). Applicant submits with this response a sequence listing as required under 37 C.F.R. 1.821. Applicant believes this objection has been overcome and respectfully request its withdrawal.

Double Patenting

The examiner has provisionally rejected claim 1 under the judicially created doctrine of obviousness-type double patenting over claims 1-6, 8-12, 18, and 20 of application SN 09/963,038. Applicants respectfully traverse the rejection. In order for a double patenting rejection to be made a determination must be made as to whether the claims of the applications at issue are not patentably distinct (i.e., obvious variations). The claims in the present application are drawn to an isolated peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA, wherein the peptide is a multiple antigenic peptide. Additional claim is made to multiple antigenic peptides, wherein the multiple antigenic peptide has at least one first arm comprising the amino acid sequence of SEQ ID NO: 5, at least one second arm comprising the amino acid sequence of SEQ ID NO:6, and at least one third arm comprising the amino acid sequence of SEQ ID NO:7. The claims in SN 09/963,038 are drawn to a peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA. Claims in the co-pending application also describe SEQ ID NO: 5, 6, and 7. The Examiner alleges that because the claims are overlapping in scope they are not patentably distinct. Although it is possible that the claims of application SN 09/963,038 may dominate the claims of the present application, the claims of application SN 09/963,038 neither describe nor suggest multiple antigenic peptides (i.e., there is no mention of peptides with a branched structure in the claims or specification). As the claims in the present application are only drawn to multiple antigenic peptides, the present application is clearly drawn to an independent, distinct, and unobvious invention. Furthermore, it is clear from the Office Action that the Examiner has misconstrued the meaning of multiple antigenic peptide to include linear constructs. However, as the term is used in the application and understood in the art, a multiple antigenic peptide is a branching structure comprising two or more arms (see below). As such a structure is not

claimed in SN 09/963,038, double patenting can not occur. Applicants believe the rejection to be overcome and respectfully request that it be withdrawn.

Rejection Under 35 U.S.C. § 101

Claim 1 has been rejected under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. Specifically, the examiner alleges that the claim as written encompasses naturally occurring peptides. Applicant respectfully traverses this rejection. Applicant has amended claim 1 to recite "An isolated peptide." Support for this amendment can be found at least on page 23, line 24. Applicant believes that this amendment in no way narrows the scope of the claim as the claim was clear as previously written. Applicant believes this rejection to be overcome and respectfully requests its withdrawal.

35 U.S.C. § 112, ¶ 2

Claims 1 and 11 are rejected under 35 U.S.C. § 112, ¶ 2 for allegedly being indefinite. In particular claim 1 has been rejected for allegedly being indefinite for the use of the abbreviation "PsaA." Applicants have amended to the claims to recite "...an animal with *Streptococcus pneumoniae* pneumococcal surface adhesion A protein (PsaA), wherein the peptide is a multiple antigenic peptide." Support for this amendment is found in the original language of claim 1 and at least in the specification on page 1, lines 5 to 8 and page 2, lines 4 to 6. Applicants believe this rejection has been overcome and respectfully request its withdrawal. This amendment neither narrows the claim nor was made for reasons related to patentability as the claims were clear and unambiguous as written before.

Claim 11 has been rejected for allegedly being indefinite for the recitation of "comprising SEQ ID NO:" without reciting that the sequence is an amino acid sequence. Applicants believe that the rejection is unwarranted as the claim must be read in light of what would be understood by those of ordinary skill in the art. It is clear that those of ordinary skill in the art would know that peptides are composed of amino acids and would know that the sequences referred to in the

claims were amino acid sequences. Furthermore, upon examining the sequences themselves, it would be clear to those of ordinary skill in the art that the sequences are amino acid sequences. However, to expedite prosecution of the present application, claim 11 has been amended to recite "comprising the amino acid sequence of SEQ ID NO:..." Support for this amendment is found in the original language of claim 11 and at least in the specification on page 4, lines 10-19. Applicants believe this rejection has been overcome and respectfully request its withdrawal. This amendment neither narrows the claim nor was made for reasons related to patentability as the claims were clear and unambiguous as written before.

Claim 11 has also been rejected as allegedly being indefinite for use of the term "arm." The Examiner asserts that it is unclear what is encompassed by the term "arm." Applicant respectfully traverses this rejection. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: a) the content of the particular application disclosure; b) the teachings of the prior art; and c) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP 2173.02). The term "arm" is well known in the art of multiple antigenic peptides (MAP). See, for example, Reynolds et al., (1994) J. Immunol. 152: 193-200 (attached as exhibit A), in particular, page 193 second paragraph and Figure 4 which uses "arm" in a context in which it clearly means individual epitopes linked together in a common branching structure. See also, Johnson et al., (2002) J. Inf. Dis. 185: 489-496 (attached as exhibit B), in particular, page 490, column 2, second paragraph through page 491, first paragraph and Figure 4. Thus, this term is clearly understood by those of skill in the art. In considering whether the claim apprises one of skill in the art of its scope (MPEP 2173.02) these facts alone, support the conclusion that it does Additionally, throughout the specification and at least on page 4, lines 24 to 31; page 5, lines 1 to 24; page 7, lines 4 to 13; page 32, line 1 through page 33 line 9; page 64, line 24 through page 65, line 4, page 67, lines 2 to 10; and Figure 1 applicant clearly exemplifies, depicts, and describes "arm" in a context and manner that would be understood by the skilled artisan in this field. As the term "arm" is clearly described in the specification and is clearly understood in the art, applicant believes that no

further modification of the claim is necessary. Applicant believes this rejection is overcome and respectfully requests its withdrawal.

Rejection Under 35 U.S.C. § 102

Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by De et al., (1999) Pathobiology 67:115-122. Claims 1 and 11 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ades et al., WO 99/45121. Applicants respectfully traverse these rejections. Applicants point out that in order for a publication or patent to anticipate a claim, each and every element of the claim must be present in the patent or publication either explicitly or inherently. The present claims are drawn to multiple antigenic peptides. In the rejection, the Examiner has misconstrued the meaning of multiple antigenic peptide to include polypeptides. "Polypeptide" as clearly intended by De refers to a protein. Although any protein can have many epitopes within its sequence, the Examiner's broad interpretation of a polypeptide or protein as a multiple antigenic peptide would necessitate any protein being referred to as a multiple antigenic peptide. However, such an interpretation is not commensurate with the definition of multiple antigenic peptide as understood in the art. The term "multiple antigenic peptide" (MAP) is clearly understood in the art to mean a branching peptide construct comprising more than one arm, each of which is a separate peptide, each possessing antigenic properties (See, for example, Reynolds et al., (1994) J. Immunol. 152: 193-200, and Johnson et al., (2002) J. Inf. Dis. 185: 489-496). This definition is also clearly the intent of the applicants as noted on page 32, line 2 through page 33, line 9. Such a construct is not present or described in De et al. As this publication does not disclose multiple antigenic peptides, it can not anticipate the claims. The same argument may be made in reference to the PCT publication WO 99/45121. Though WO 99/45121 does disclose SEQ ID NO: 5, 6, and 7, the publication does not disclose multiple antigenic peptides. As such, the publication can not anticipate the claims as written. Applicants believe the rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

Payment in the amount of $410.00 for the 2-month extension of time is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled. Credit Card Payment Form PTO-2038. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional amount or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Gwendolyn D. Spratt
Reg. No. 36,016

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
404/688-0770
404/688-9880 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence and any items indicated as attached or included is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Gwendolyn D. Spratt — Date: February 19, 2003

Marked Up Version of Amended Specification
Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

Please replace the paragraph at page 28, lines 11 to 23 with the following amended paragraph:

Many adjuvants are known in the art that could be used to stimulate an immune response to peptides of the current invention. For example, alum, proteosomes, certain lipids, such as palmitic acid (see below), QS21, or [alhydrogel] ALHYDROGEL ® (2%; #A1090BS, Accurate Chemical and Scientific Company, Westbury, NY) could be used as an adjuvant in the present invention (da Fonseca, D. P., et al., "Identification of new cytotoxic T-cell epitopes on the 38-kilodalton lipoglycoprotein of Mycobacterium tuberculosis by using lipopeptides," *Infect. Immun.* 66:3190 (1998); Sheikh, N. A., et al., "Generation of antigen specific CD8+ cytotoxic T cells following immunization with soluble protein formulated with novel glycoside adjuvants," *Vaccine* 17:2974 (1999); and Moore, A., et al., "The adjuvant combination monophosphoryl lipid A and QS21 switches T cell responses induced with a soluble recombinant HIV protein from Th2 to Th1," *Vaccine* 17: 2517 (1999).

Please replace the paragraph at page 35, line 21 through page 36, line 10 with the following amended paragraph:

ELISA. Screening of hybridoma culture supernatants was done by ELISA. U-bottom microtitration plates (Costar, Cambridge, Mass.) were sensitized with 50 µl of *S. pneumoniae* whole cell suspension (10^9 cfu/ml) diluted 1:4,000 in 0.1 M carbonate buffer, pH 9.6, and kept for 16 h at 4°C. The plates were washed 5 times with 0.9% NaCl containing 0.05% [Tween] TWEEN ® -20 (NaCl-T). Culture supernatants (50 µl) from the fusion plates were added to 50 µl of a solution containing 2% bovine serum albumin (BSA). 10% normal rabbit serum, 0.3% [Tween] TWEEN ®-20, and 0.02% Merthiolate in phosphate buffered saline (PBS), pH 7.2, (ELISA diluent, Wells et al. (1987) *J. Clin. Microbiol.* 25:516-521) in the plates and

were incubated for 30 min at 37°C. The plates were washed 5 times with NaCl-T. Fifty microliters of goat anti-mouse immunoglobulin horseradish peroxidase conjugate in ELISA diluent was added to each well. The plates were incubated for 30 min at 37°C. The plates were washed, and 50 µl of 3,3',5,5'-tetramethylbenzidine (0.1 mg/ml in 0.1M sodium acetate, 0.1 M citric acid (pH 5.7) with 0.005% hydrogen peroxide) was added to each well and incubated for 30 min at 37°C. The reaction was stopped by adding 1 ml of 4 M H_2SO_4 and the optical density was read on a Dynatech ELISA Reader (Dynatech Laboratories, Inc., Alexandria, Va.) at 450 nm. An optical density of greater than 0. 200 was considered positive.

Please replace the paragraph at page 36, line 11 through page 37, line 10 with the following amended paragraph:

SDS-PAGE and immunoblot analysis. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed by the method of Tsang et al. ((1983) *Methods Enzymol.*, 92:377-391), using an 8% acrylamide resolving gel. Equal volumes of sample buffer (5% SDS-10% 2-mercaptoethanol-20% glycerol in 0.01 M Tris HC1, pH 8.0) and cell suspension containing 2.4 µg protein per µl were mixed, heated at 100°C for 5 min, and a 5-µl sample was applied to 1 of 15 wells. If the final protein content of the portion of sample to be tested was <1.2 µg/µl, a volume up to 10 µl of sample was applied to achieve a final concentration of 6 µl of protein per well. Protein concentrations were determined by the method of Markwell et al. ((1978), *Anal. Biochem.* 87:206-210), with BSA as the standard. Proteins separated by SDS-PAGE were either silver stained by the method of Morrissey ((1981) *Anal. Biochem.* 117:307-310) or electroblotted onto nitrocellulose (Schleicher & Schuell, Inc., Keene, N.H.). The immunoblot procedure was done according to the method of Tsang et al. (1983) with slight modifications. The blots were given three 5-min washes with PBS, pH 7.2, containing 0.3% [Tween] TWEEN ®-20 and were gently agitated overnight (16 h) at 25°C. The blots were blocked for 1 h with casein-thimerosal buffer (CTB) (Kenna et al. (1985) *J. Immunol Meth.*, 85:409-419). After three rinses with CTB, the blots were exposed to goat anti-mouse

immunoglobulin horseradish peroxidase conjugate (Bio-Rad Laboratories, Richmond, Calif) for 2 h at 25°C. Conjugate dilutions (1:2,000) were made in CTB. The blots were again rinsed three times with CTB and exposed to 3,3'-diaminobenzidine-4-hydrochloride in PBS, pH 7.2 (0.5 mg/ml), with 0.003% H_2O_2 for 5 min at 25°C. Reactivity was expressed as a visible colored band on the nitrocellulose paper. Low molecular-mass protein standards (Bio-Rad) were used in PAGE and immunoblotting. Rabbit antisera to the protein standards were used to develop the standards (Carlone (1986) *Anal. Biochem.* 155:89-91). Molecular masses were calculated by the method of Neville et al. ((1974), *Methods Enzymol.* 32:92-102) using appropriate molecular mass standards.

Please replace the paragraph at page 37, lines 11 to 26 with the following amended paragraph:

Immunofluorescence Assays. A bacterial suspension containing approximately 400-500 cfu per field (10 µl) was allowed to dry at room temperature on each well of acetone-resistant, 12-well (5 mm diameter), glass slides (25 x 75 mm) (Cel-Line Associates, Newfield, N.J.). The slides were then immersed in acetone for 10 min and air dried at room temperature. MAbs were added to the slides, which were incubated for 30 min at 37°C. After incubation, the slides were gently rinsed with PBS and soaked twice at 5-min intervals, blotted on filter paper, and air dried at room temperature. Fluorescein-labeled rabbit anti-mouse immunoglobulin (courtesy of W. F. Bibb, CDC) was then added, and the slides were incubated for 30 min at 37°C. They were then washed twice with PBS and gently blotted on filter paper. Slides were covered with carbonate-buffered mounting fluid, pH 9.0, and cover slips and were then read with a [Leitz Dialux] LEITZ DIALUX ® 20 fluorescence microscope equipped with a HBO-100 mercury incident light source, an I cube filter system, a 40x dry objective lens, and 6.3x binoculars (Leitz, Inc., Rockleigh, N.J.).

Please replace the paragraph at page 37, line 27 through page 38, line 25 with the following amended paragraph:

Immunoelectron-microscopy. Pneumococcal cells were washed two times with PBS and fixed in a freshly made mixture of 1% paraformaldehyde-0.1% glutaraldehyde for 20 min at 4°C. The cells were dehydrated in a graded alcohol series and then in a 1:1 mixture of absolute ethanol and [Lowicryl] LOWICRYL® K4M (Ladd Research Industries, Inc., Burlington, Vt.) for 1 h at 4°C. The cells were pelleted and suspended in a 1:2 mixture of absolute ethanol and [Lowicryl] LOWICRYL® K4M for 1 h at 4°C. They were again pelleted and suspended in [Lowicryl] LOWICRYL® K4M (undiluted) for 16 h at 4°C. The cells were transferred to fresh and undiluted [Lowicryl] LOWICRYL® K4M two times during the next 24-hour period. The [Lowicryl] LOWICRYL® K4M-treated cells were imbedded in gelatin capsules and placed in a box lined with aluminum foil. The capsules were hardened using a short-wave UV light source (35 cm distance for 72 h at -20°C). The box was brought to room temperature, and the capsules were allowed to continue hardening for up to 14 days. Samples of the capsule were cut into 100-μm thin sections and picked up on nickel grids. Grids containing the sample were placed on a droplet of ovalbumin solution in PBS containing sodium azide (E.Y. Laboratories, Inc., San Mateo, Calif) for 5 min The grids (wet) were transferred to a solution of primary MAbs diluted in a solution of BSA reagent (1% BSA in PBS containing 0.1% TRITON X- 100™, [Tween] TWEEN ® -20, and sodium azide) (E. Y. Laboratories) and incubated for 1 h at room temperature or 18 to 48 h at 4°C in a moist chamber. For antibody binding controls, other grids were wetted with MAbs against *Legionella pneumophila*. The grids were rinsed two times with PBS and incubated on droplets of goat anti-mouse IgG-labeled colloidal cold particles (20 μm)(E. Y. Laboratories) for 1 h at room temperature. The grids were rinsed two times and post-stained with osmium tetroxide, uranyl acetate, and lead citrate. The grids were examined with a Philips 410 transmission electron microscope.

Please replace the paragraph at page 57, lines 9 to 24 with the following amended paragraph:

High affinity specimens from the library obtained using the procedures of Example 11 were propagated and sequenced. For each MAb, ten phage specimens resulting from the selection process were sequenced. Approximately 1 μg of single-stranded DNA was purified by phenol and chloroform extraction, ethanol precipitated and resuspended in 7 μl water. Sequencing reactions were performed using a 27-mer primer complementary to the FUSE 5 vector sequence derived from a region in wild-type pIII common to all fd-tet derived vectors and ^{35}S [Sequenase] SEQUENASE® version 2 (U.S. Biochemicals, Cleveland, OH). The sequences obtained are shown in Table 4. They were compared to known sequences of PsaA strains 2 and 6B using Clusta IV and tFasta programs to identify the epitope on the PsaA with which each peptide is aligned most closely. These epitope positions are also given in Table 4. The peptide obtained using MAb's 8G12, 6F6, and 1E7 align to PsaA best when an additional residue is present on the protein where the gap appears after residue 13 of the peptide (SEQ ID NO: 7 and SEQ ID NO: 8).

Please replace the paragraph at page 60, lines 1 to 11 with the following amended paragraph:

Anti-PsaA specific ELISA was performed as follows: Nunc immuno MaxiSorb™ plates were coated with 5 μg/ml of purified native PsaA protein at 4°C overnight. Plates were washed with PBS/Tween buffer (PBS containing 0.01% [Tween] TWEEN ®-20) and blocked with PBS/Tween buffer containing 1% BSA. Serial dilutions of mouse sera starting at 1:10 in PBS/Tween/BSA were incubated for 1 h at 37°C. The plates were washed four times with PBS/Tween. Anti-mouse IgG and IgM conjugated to horseradish peroxidase (Sigma, St. Louis, MO), diluted at 1:4000 in PBS/Tween/BSA, were added to the plates. Anti-PsaA antibodies

were detected with *o*-phenylenediamine substrate for 30 min in the dark. Absorbance was read at 490 nm on Microplate E1311 (Biotek, Winooski, VT).

Please replace the paragraph at page 62, line 25 through page 63, line 21 with the following amended paragraph:

To analyze the ability of the peptide SEQ ID NO: 5-lipidated and SEQ ID NO:5-unlipidated to protect against *S. pneumoniae* challenge, ten-week-old ND-4 mice (Swiss Webster) were immunized on a three-dose regimen. Test mice (n = 15 for each peptide) received an initial dose at Day 0 of 100 μg followed by booster doses at 3 and 5 weeks of 50 μg of the appropriate peptide. The peptide SEQ ID NO: 5-lipidated was suspended in 100 μl PBS 0.01 M, pH 7.2, while the unlipidated peptide SEQ ID NO: 5-unlipidated, was mixed with the adjuvant [alhydrogel] ALHYDROGEL ® (2%; #A1090BS, Accurate Chemical and Scientific Company, Westbury, NY) at 6.3 mg/ml in PBS to enhance the immunogenicity of the peptide. Control mice (n = 12) were similarly immunized but without peptide. Each mouse was immunized subcutaneously between the shoulders. One week following the final boost, all mice were challenged with 4.9×10^6 cfu of *S. pneumoniae*, strain PLN-D39 (kindly provided by James Paton, Women's and Children's Hospital, North Adelaide, S.A. Australia), a pneumolysin-negative derivative of D39. This was followed 5 days later by euthanasia and culturing of nasal washes. PBS nasal washes were done by the method of Wu, H.Y., et al., ("Establishment of a *Streptococcus pneumoniae* nasopharyngeal colonization model in adult mice," *Microb. Pathog.* 23:127 (1997)). The wash was diluted 3x out to a final dilution of 1:486. Fifty microliters of each dilution was cultured on blood agar + gentamicin plates (Trypticase soy agar supplemented with 5% defibrinated sheep blood and 0.5% gentamicin). Data from NP colonization and carriage in immunized mice and placebo (PBS-immunized controls) were analyzed using either the t-test or the Mann-Whitney rank sum test. Nasopharyngeal carriage is the number of colony forming units per nose. Nasopharyngeal colonization is either positive or negative for a mouse depending on whether at least 1 cfu forms in 25 μl of nasal wash.

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A isolated peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *Streptococcus pneumoniae* pneumococcal surface adhesion A protein (PsaA), wherein the peptide is a multiple antigenic peptide.

11. (Amended) The peptide of claim [2] 1, wherein the multiple antigenic peptide has at least one first arm comprising the amino acid sequence of SEQ ID NO: 5, at least one second arm comprising the amino acid sequence of SEQ ID NO:6, and at least one third arm comprising the amino acid sequence of SEQ ID NO:7.